UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/533,726 | 10/25/2006 | Rajiv Khanna | 0069518-000002 | 7355 |

21839 7590 10/11/2007

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

| EXAMINER | |
|---|---|
| LUCAS, ZACHARIAH | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 10/11/2007 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com
debra.hawkins@bipc.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/533,726 | KHANNA ET AL. | |
| | Examiner | Art Unit | |
| | Zachariah Lucas | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17,27-29,34,36-38 and 42-46* is/are pending in the application.

4a) Of the above claim(s) *2, 3, 5, and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-17,27-29,34,36-38 and 42-46* is/are rejected.

7)☒ Claim(s) *1, 4, 7, and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-17, 27-29, 34, 36-38, and 42-46 are pending in the application.

### *Election/Restrictions*

2. Applicant's election without traverse of the sequences SEQ ID NO: 6, SEQ ID NO: 21, SEQ ID NO: 41, and embodiments wherein the EBV associated disease is a lymphoepithelioma-like carcinoma (including NPC) in the reply filed on September 9, 2007 is acknowledged.

3. Claims 2, 3, 5, and 6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 9, 2007.

4. Claims 1, 4, 7-17, 27-29, 34, 36-38, and 42-46 are under consideration.

### *Information Disclosure Statement*

5. The information disclosure statement (IDS) submitted on May 4, 2007 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

### *Drawings*

6. The drawings are objected to because the information is the darkened portions of Figure 8 are not legible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the

sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Specification***

7. The specification is objected to for containing referring to sequences without also identifying them by the sequence identifier assigned to them in the sequence listing as required by 37 CFR 1.821(d). See, Figures 3, 4, and 7 (and pages 9, lines 11-20, 10, lines 5-12, - providing the Brief Descriptions thereof), and Tables 2-5, pages 45-50. The examiner would like to bring the applicant's attention to the following excerpt from MPEP §2422.03:

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing." Where a sequence is embedded in the text of an application, it must be presented in a manner that complies with the requirements of the sequence rules.

The applicant is therefore required to amend the specification to comply with 37 CFR 1.821(d). With respect to the Figures, the sequence identification numbers may be provided in either the Figure, or the Brief Summary thereof.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 9-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on variants of identified EBV CTL epitopes. The specification defines such variants as comprising one or more deletions or substitutions "without substantial alteration to immunogenicity." These claims are rejected as indefinite because it is not clear what is meant by the quoted phrase. It is not clear what the Applicant considers to be a substantial alteration to immunogenicity in that a modification to the epitope may cause different types and levels of changes to immunogenicity.

In one instance, a change may result in the CTL response targeting one protein or peptide instead of another. Different levels of such changes may include changing the response from EBV to another virus, or from one EBV to another EBV. I

In another instance, the changes may merely affect the ability of the variant to induce an anti-EBV immune response.

It is not clear from the application what the scope of variants claimed is because it is not clear if the term is intended to include variants that result in one type of the changes in

immunogenicity described above, and not the other; or the extent of changes to immunogenicity that is intended from the use of the term "substantial." The claims are therefore rejected as indefinite.

With respect to claims 9 and 10, it is also noted that the definition of the term "variant" in the specification indicates that a variant has one or more deletions or substitutions relative to the respective EBV CTL epitope. However, claim 9 identifies the variants of that claim as "differing by one, two or three amino acids from" the relevant epitope. It is not clear from this language if the quoted phrase is intended to define the claimed variants differently from the definition provided in the specification (i.e., such that the variant epitopes may also include additions to the indicated epitopes), or if the language is intended only to alter the number of deletions or substitutions that may be made. For the purpose of this action, the broader interpretation is applied, such that additions of one to three amino acids would be included in the claimed genus.

Claim 11 is rejected because is not clear from the claim if the phrase "having an amino acid sequence according to" SEQ ID NO: 41 is defining the claimed variant, or defining the epitope from which the claimed variant is derived. For the purposes of this action, the claim is treated as defining the epitope, not the variant.

In addition, claims 12-17 read on an isolated protein "comprising at least on EBV CTL epitope and/or a EBV CTL epitope variant according to Claim 1." Claim 1 does not disclose any epitope variants. Thus, it is not clear what variants are being referred to in these claims.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 9-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As indicated above, these claims read on variants of isolated EBV CTL epitopes. The specification defines an EBV CTL epitope as "a sequence of amino acids that is encoded by an EBV genome and is capable of eliciting" a CTL response. Page 12. As was described above, the application also defines variants of such epitopes as EBV epitopes "in which one or more amino acids have been deleted or replaced by different amino acids without substantial alteration to immunogenicity."

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

However, even the presence of multiple species with in a claimed genus does not necessarily demonstrate possession of the genus. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support).

In the present case, the application discloses three different potential EBV CTL epitopes corresponding to SEQ ID NO: 21 (including SEQ ID NO: 21 itself- see Table 4, page 48). However, each of these epitopes is identified as being isolated from an isolate of EBV. Thus, the only examples of any variants of the disclosed EBV CTL epitopes in the application are themselves EBV epitopes.

Further, the application fails to show that the potential epitopes are variants as defined by the present application in that the application does not demonstrate that the variant forms of SEQ ID NO: 21 either retain the ability to induce an immune response against SEQ ID NO: 21 (i.e. failed to show cross-reactivity among the isolates) or that the changes to the sequence had no or

little effect on the ability of the peptide to induce an immune response, each of which would be required to demonstrate that the variants had no "substantial alteration to immunogenicity."

While the application provides no demonstrations regarding the effects of variations in the elected peptide of SEQ ID NO: 21, it is noted that the application demonstrated that changes in the sequence of another peptide did have substantial affects on the immunogenicity of the epitope. See e.g., pages 32-33, and 37-38. Thus, the teachings of the application itself demonstrates uncertainty as to the effects of variations to the disclosed epitopes such that those in the art would be capable of distinguishing those variants that retained the same immunological activity from those that did not. Such teachings are supported by those of the art, which indicate that a variation of an epitope in one EBV such that it corresponds to the sequence of another EBV isolate, may result in the "loss" of the epitope. See e.g., Lin et al., J Biomed Sci 12:925-36, at 934 (last paragraph in right column). Thus, the teachings in the application and the art indicate uncertainty as to the effects of variations to an identified epitope, and indicate that even peptides representing sequences from other EBV isolates corresponding to an identified EBV epitope fail to retain the immunogenic properties of the identified epitope.

In view of the lack of any examples of EBV variants that are not themselves derived from EBV isolates, any demonstration of variants of SEQ ID NO: 21 that retain the same immunogenicity as SEQ ID NO: 21, and in view of the uncertainty as to whether any particular variant would meet the requirement that the variants are "without substantial alteration to immunogenicity," the claims are rejected as lacking adequate antecedent basis support for the claimed genus of EBV epitope variants.

12. Claims 27-29, 34, 36-38, and 42-46 are rejected while being enabling for immunogenic compositions comprising the indicated epitope or methods of inducing anti-EBV T-cell response using such, does not reasonably provide enablement for methods of treating or preventing nasopharyngeal carcinoma (NPC), wherein the methods comprise the administration of EBV latent protein epitopes, or pharmaceutical compositions comprising the epitopes.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, those factors considered most relevant are the direction and guidance presented, the presence or absence of working examples, the state of the prior art, and the breadth of the claims.

Claims 27-29 are drawn to pharmaceutical compositions comprising the epitope of SEQ ID NO: 21, or a polyepitope protein of SEQ ID NO: 81 (which comprises SEQ ID NO: 21). The remaining claims under rejection are drawn to methods of treating or preventing EBV-associated diseases, esp. nasopharyngeal carcinoma (NPC), comprising the administration of SEQ ID NO: 21 or a polyepitope protein comprising this sequence.

In support of these claims, the application provides examples of potential T-cell epitopes, and demonstrates the induction of T-cell responses against the epitope of SEQ ID NO: 21. However, the application does not demonstrate that T-cells targeting any of the disclosed epitopes are capable of killing NPC cells, or of permitting the treatment or prevention of NPC.

The teachings in the art indicate that, while CTL based therapies may be useful in the treatment of NPC, there are still several basis of uncertainty as to the effects such therapies would have, and as what epitopes would be used in these therapies. See e.g., Lee et al., Sem Cancer Biol 12: 463-71, at page 469. Moreover, while certain teachings in the art indicate that compositions based on a polyepitope protein were capable of inducing therapeutic and protective responses against certain EBV-associated diseases, the compositions actually administered were not individual epitopes or even polyepitope proteins, but were viral vectors resulting in the immunogenic expression of a polyepitope protein. See e.g., Duraiswamy et al., Blood 101: 3150-56, 2003 (Duraiswamy 2003- of record in the May 2005 IDS) and Duraiswamy et al., Cancer Res 64: 1483-89, 2004 (Duraiswamy 2004). In addition, the references also indicate that the proteins against which the immune response is being induced are poorly immunogenic. See e.g., Duraiswamy 2004 at 1488 (left column). Duraiswamy 2004 also indicates that the mouse results seen in the reference are not necessarily indicative of therapeutic responses in humans. See e.g., page 3155, right column. This reference both indicates that there are other obstacles and complexities that are likely to inhibit success in humans, including the delivery modality and the immunosuppressive nature of the target diseases. Thus, the reference indicates that the operability of even these compositions, which were developed to overcome limitations in prior vaccine compositions, was uncertain.

Moreover, in addition to the uncertainties of the disclosed polyepitope vaccines, the references also indicate that inclusion of epitopes other than HLA class I epitopes such as SEQ ID NO: 21) are likely to be required for effective usage in the treatment or prevention of the target diseases in normal populations (whereas in the mouse models used, the mice were designed to express particular HLA molecules recognizing the epitopes used in the experimental vaccine). Thus, instead of indicating that the present claims are likely to be effective, the cited references provide several basis both for distinction from the presently claimed methods, and indicating uncertainty as to their operation in treating or preventing the EBV-associated diseases in humans. This seen particularly well where the Duraiswamy 2003 reference concludes that the teachings therein provide a platform for the future development of immunotherapies against EBV-associated disorders, but does not conclude that the vaccines actually described therein would be effective.

In view of the limited teachings of the present application, the teachings in the art indicating uncertainty in the operation of the claimed methods and intended uses of the claimed compositions, the indicated claims are rejected for exceeding the scope for which an enabling disclosure has been provided.

### *Claim Rejections - 35 USC § 102*

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Thorley-Lawson et al. (PNAS 84:5384-88- reference AF in the May 2005 IDS). These claims are drawn to variants of an isolated EBV epitope that consists of an amino acid sequence differing from (e.g.) SEQ ID NO: 1 by one, two or three amino acids. The limitations of this claim have been described above. See, rejection under 35 U.S.C. 112, second paragraph. The reference discloses on page 5385 a peptide consisting of a sequence that varies from SEQ ID NO: 1 by two amino acid residues (the addition of a C and a L to the N-terminal). The peptide is identified as capable of inducing a CTL response against EBV (albeit at low frequencies). The reference therefore anticipates the indicated claims.

15. Claims 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Miller et al. (Oncogene 16: 1869-1877). These claims are drawn to isolated proteins comprising at least one, or a plurality of EBV CTL epitopes, wherein SEQ ID NO: 21 is present in the protein. Such a protein is disclosed by this reference. See e.g., Figure 3 (teaching isolated EBV C15 derived LMP1 proteins). See also, GenPept Accession AAD01758, showing that this LMP1 protein comprises SEQ ID NO: 21 at positions 156-164. Cf. present claim 14. The reference therefore anticipates the indicated claims.

***Conclusion***

16. No claims are allowed. Claims 1, 4, 7, and 8 are objected to for including non-elected inventions. It is noted that the various other epitopes share not common special technical feature with the elected epitopes.

17. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> U.S. 2006/0204514 (publication of patent application 10/521010) This published application contains claims overlapping with the present claims. Because these applications have different inventive entities, and claim overlapping subject matter, the other application may represent a subject of potential interference with the present application. See e.g., claim 22 of the reference. The reference is not considered prior art to the present application.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Z. Lucas/
Patent Examiner, AU 1648